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REVIEW

The incidence and prevalence of thyroid autoimmunity

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Abstract The thyroid gland is the most common organ affected by autoimmune disease. Other autoimmune diseases, most notably type 1 diabetes mellitus, are increasing in incidence. It is unknown whether autoimmune thyroid diseases are following the same pattern. This review summarizes studies of autoimmune thyroid disease incidence and prevalence since 1950, not only for these measures of occurrences, but also for commenting on identified risk factors for thyroid autoimmunity. We find that incidence of autoimmune thyroid disease is currently higher than in historic series although the studies are so variable in design, patient population, disease definition, and laboratory methods that it is impossible to tell whether this difference is real. Further research is required to assess the possibility of changing disease patterns of autoimmune thyroid disease as opposed to simple changes in diagnostic thresholds.

Keywords Hashimoto disease · Graves disease · Autoantibodies · Incidence · Prevalence

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Introduction

Autoimmune disease affects the thyroid more than any other organ [1]. Autoimmune thyroid disease (AITD) encompasses a closely related spectrum of disorders, representing two clusters of pathogenic mechanisms. Hashimoto's disease (a term we use synonymously with chronic autoimmune thyroiditis and autoimmune hypothyroidism) and post-partum thyroiditis/painless thyroiditis share a predominately T cell-mediated autoimmunity, while Graves' disease is characterized by a primarily humoral response and the presence of anti-thyroid stimulating hormone (TSH) receptor antibodies [2]. All forms of AITD are associated with the formation of serum thyroid peroxidase (TPO) and thyroglobulin (Tg) antibodies. Underlying autoimmunity without clinical autoimmune disease is diagnosed by the presence of these antibodies.

The incidence of other autoimmune endocrine disorders, particularly type 1 diabetes mellitus, has markedly risen in recent years [3]. The cause of this rising incidence is unexplained, but raises the question of whether the frequency of thyroid autoimmunity may be also following the same trend. In this, the 100th anniversary of Hashimoto's original description of the disease that now bears his name [4], we have reviewed studies assessing the incidence and prevalence of thyroid autoimmunity, Hashimoto's disease, and Graves' disease throughout the world, starting from 1950. In summarizing the literature, we also hope to highlight gaps in our knowledge requiring fresh investigation. It is important to be aware of the burden of AITD, its geographic differences, and trends over time. This knowledge will provide clues to confirming AITD etiology, may help in estimating changes in epidemiology of associated conditions, and will provide data for health utilization projections in future.

We are aware of several recent reviews relevant to the epidemiology of autoimmune thyroid disorders. The study by McGrogan et al. [5] is complementary to ours although there are several important differences. That study features two aspects not included in our paper: (1) overall estimates for the incidence of all autoimmune thyroid disorders, which we have chosen not to do (see below); and (2) estimates of non-autoimmune thyroid diseases (e.g., toxic nodular disease in hyperthyroidism) were included in some papers' reports of incidence rates. We have also chosen to take a more descriptive approach to the identified studies: (1) to explore factors that may impact on the incidence of autoimmune thyroid disease, (2) to emphasize geographic differences among studies, and (3) to include data on thyroid antibody prevalence. Our review also includes discussion of some important incidence studies not included in the study by McGrogan et al. Vanderpump [6] recently reviewed the epidemiology of thyroid diseases, which include AITD, although autoimmunity was not the focus of his paper. Nicholson et al. [7] systematically reviewed the incidence of post-partum thyroid dysfunction, which is outside of the scope of our review.

Search strategy & review methods

We searched PubMed (National Library of Medicine, Bethesda, MD) from 1950 to February 2012 for English language studies using terms "autoimmune thyroid," "autoimmune hypothyroidism," "Hashimot*," "thyroiditis," "thyroid autoantibodies," "autoantibody analysis," "Graves*," "incidence," and "prevalence." In selecting relevant studies, abstracts were screened for potentially relevant papers, after which full texts were assessed. We also examined reference lists of included articles and review articles captured by the PubMed search for previously unidentified studies.

To maximize comparability of studies, we used a prespecified inclusion criterion of original research studies assessing incidence or prevalence of Hashimoto's disease (including antibody positivity) and Graves' disease in population-based samples or unselected cohorts. Pediatric- and geriatric-only studies were excluded. Studies assessing clinical hyperthyroidism must have distinguished between Graves' and toxic nodular disease to be included. Studies assessing clinical hypothyroidism must have either made attempts to distinguish etiology, for example by measuring thyroid antibodies, or reported on spontaneous overt hypothyroidism.

Because the identified studies were so variable in design, patient population, disease definition, and laboratory methods (see "Synthesis and conclusions" section), a quantitative synthesis has not been performed; instead, we have taken a descriptive approach. We grouped studies based on disease assessed (either Hashimoto's disease/antibody status or Graves' disease) and then by geographical region, starting with the region with the earliest studies. We then describe studies from that region chronologically. While it could be argued that thyroid antibody positivity (i.e., thyroid autoimmunity without known autoimmune disease) should be treated separately from Hashimoto's disease, many studies addressing antibody positivity intertwined their results with the clinical diagnosis and analyzed the relationship between antibody status and hypothyroidism. Thus, to keep the description coherent, we report these studies together. Space considerations prevent a detailed description of all identified studies, especially those dealing exclusively with antibody prevalence and those addressing Graves' disease, with only those we judged to be the most informative presented in the text. We have, however, listed all other identified studies in Supplemental Tables 1–4 for the readers' reference (Supplemental Table 1 describes the studies assessing incidence of Hashimoto's thyroiditis, Supplemental Table 2 enumerates the studies assessing thyroid autoantibody prevalence, Supplemental Table 3 lists the studies assessing the prevalence Hashimoto's disease and autoimmune hypothyroidism, and Supplemental Table 4 details the studies assessing incidence of Graves' disease). Where antibody prevalence data were discussed in the text, we generally tried to use TPO/microsomal antibody for consistency and comparability, although again, Tg antibody data are enumerated in the Supplemental tables.

Hashimoto's disease, including antibody positivity

Europe

UK

The first population-based study of thyroid antibody positivity was performed in Northern England in 1962–1963 [8]. Tg antibodies were measured on adults over 21 years of age by means of hemagglutination. 16.2 % of females and 4.3 % of males tested positive with higher prevalence as age increased until after the seventh decade. The much higher prevalence of Tg antibodies in this study, compared to the later Whickham survey, has been ascribed to changes in assay technique. However, a similar prevalence was reported by Jacobs et al. (published in 1969), who assessed antibodies to thyroid tissue using indirect immunofluorescence microscopy with 14.6 % of females and 5.2 % of males having positive results [9].

The Whickham survey was the first population-based prospective cohort study to assess thyroid disease and

remains the classic epidemiologic investigation of thyroid autoimmunity. 2,779 participants from Northern England were recruited in the early 1970s. Cross-sectional results were reported initially [10] with subsequent papers examining a subcohort of patients at 4 years [11] and, finally, follow-up of the near-complete cohort at 20 years [12]. With special reference to autoimmune thyroiditis, 10.3 % of women and 2.7 % of men had thyroid cytoplasmic antibodies at baseline with the prevalence increasing markedly in women above the age of 45 years. Thyroid stimulating hormone (TSH) levels also rose with age in females, and, importantly, this escalation was abolished when those with positive thyroid antibodies were excluded from the analysis. In the early follow-up study [11], all patients with overt hypothyroidism (defined as clinically diagnosed hypothyroidism) had positive antibodies at baseline and almost all had had elevated serum TSH (defined as greater than 6 mU/L with a number of these patients having had markedly elevated TSH). The investigators estimated that for patients with elevated baseline serum TSH and positive antibodies, 5 % per year developed overt hypothyroidism. After 20 years of follow-up, the incidence of spontaneous overt hypothyroidism (presumably autoimmune) in the survivors was 350 cases/100,000/year (95 % confidence interval [CI]: 280–450) in women and 60 cases/100,000/year (95 % CI: 30–120) in men. Baseline-positive thyroid antibodies were powerful predictors of future overt hypothyroidism with an odds ratio of 8 (95 % CI: 5–15) for women and 25 (95 % CI: 10–63) for men. When baseline results included both raised serum TSH (i.e., baseline subclinical hypothyroidism) and positive anti-thyroid antibodies, the odds ratios for future overt hypothyroidism were 38 (95 % CI: 22–65) for women and 173 (95 % CI: 81–370) for men [12].

Prentice et al. [13] (published in 1990) performed radioimmunoassay for thyroid antibodies in female blood donors drawn from 7 distinct British geographical regions. 20.2 % of the women tested had positive TPO antibodies with the prevalence rising with age. The prevalence varied considerably with geographic location although this was not related to iodine intake or each region's previous goiter prevalence (recorded as a surrogate for iodine status). It is not clear whether this high reported prevalence compared to prior studies was due to increased occurrence of thyroid autoimmunity, sampling differences, or assay sensitivity.

The Thyroid Epidemiology, Audit, and Research Study (TEARS) is a Scottish registry of linked administrative databases that attempts to capture all cases of hyper- and hypothyroidism within the population of Tayside, Scotland (approximately 390,000 people). Incidence data are available from 1994 with hypothyroidism trends currently published up to 2001 (hypothyroidism being defined as continuous long-term thyroid replacement therapy because

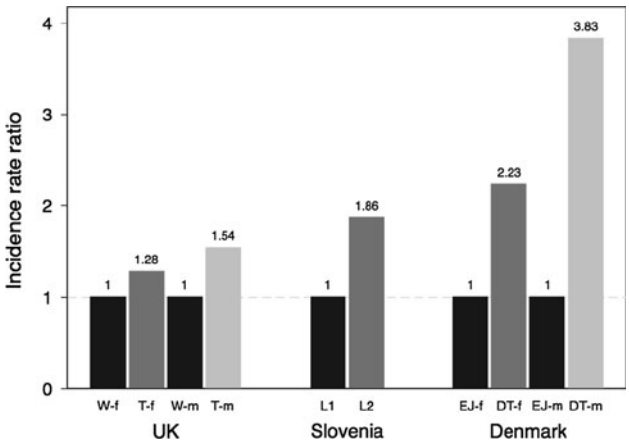

Fig. 1 Crude incidence rate ratios (IRR) for spontaneous (presumed autoimmune) hypothyroidism reported in studies performed in similar geographic locations since 1970. The baseline studies (Incidence Rate Ratio [IRR] = 1) are the first studies performed in each region. Where specific data are presented by gender, the IRR compares gender-specific rates with male and female baseline IRR = 1. IRR for *L2* versus *L1* is statistically significant (95 % confidence interval: 1.64–2.12). Statistical significance and confidence intervals cannot be constructed for other comparisons because the data are unavailable (note: a subsequent DanThyr study showed a statistically significant increase in IRR increase over time [31] although the results were not presented by hypothyroidism subtype). *W-f* Female Whickham survivors (1972–1993) [12]. *T-f* TEARS study females (1994–2001—mean standardized incidence). *W-m* Male Whickham survivors (1972–1993). *T-m* TEARS study males (1994–2001—mean standardized incidence) [14, 15]. *L1* Ljubljana (1999). *L2* Ljubljana (2009) [40]. *EJ-f* East Jutland females (1987–1998) [22]. *DT-f* DanThyr study females (1997–2000). *EJ-m* East Jutland males (1987–1998) [22]. *DT-m* DanThyr study males (1997–2000) [27]

of an underactive thyroid) [14, 15]. Because patients with a past history of thyroid surgery or hyperthyroidism are excluded from the reported data, it is assumed that almost all the cases of incident hypothyroidism are due to AITD. The study's reports thus far have noted several interesting findings: (1) the crude incidence of thyroid dysfunction appears somewhat higher than in the Whickham study—for example the mean incidence rate for hypothyroidism over the eight reported years is 448/100,000/year for women and 92/100,000/year for men (Fig. 1); (2) the incidence of hypothyroidism in males has risen over time. Hypothyroidism incidence rates in women remained unchanged through the study period, but the age of diagnosis has become significantly lower; and (3) prevalence of all forms of thyroid dysfunction has increased. Given the limitations in the data, it is unclear whether these current results reflect a true change in thyroid disease burden or alterations in medical practices.

Nordic countries

Nordic cohorts have provided the overwhelming majority of population-based studies over recent times and have greatly informed the field.

Finland The first published studies (1971 and 1972) assessed adults in two Finnish towns [16, 17]. Tg antibodies were measured by different techniques with population prevalence of 7.8 % in Ylitornio and 10.6 % in Nurmes. In clinically euthyroid patients with positive antibodies, circulating serum TSH was significantly higher than age- and sex-matched controls although the titer of antibody was not related to serum TSH level. A subsequent study by the same group, this time performed in the South of Finland, found an astonishingly high prevalence of microsomal antibodies (25.8 %) [18]. Given that the Tg antibody prevalence was comparable to the earlier study, it seems likely that either the microsomal assay (or cut-point) was nonspecific. A third study was performed in Norway in 1979 using blood donors [19]. 10.8 % of women and 3.7 % of men were considered positive for microsomal antibodies with the prevalence rising with age.

Norway Bryhni et al. [20] investigated 2,513 Norwegian adults aged 20–54 years from the iodine-replete area of Tromsø in 1979–1980 for thyroid function and antibodies with 1,939 reassessed 7 years later. The baseline prevalence of microsomal antibodies in women was 8.6 %, compared to 3.6 % in men. Prevalence increased with age. Of the 124 subjects with baseline-positive antibodies, 55 % remained positive (compared to 97 % of negative subjects remaining negative). The majority of those who became negative (60 %) had low titers of positive antibodies. A 2.9 % per year incidence of hypothyroidism developed exclusively in the antibody-positive group.

Bjøro et al. [21] performed a population-based study of 65,360 adults between 1995 and 1997 in Nord-Trøndelag, Norway. The prevalence of hypothyroidism was 4.8 % for women and 0.9 % for men. When serum TSH was above 10 mU/L, more than 85 % of patients were anti-TPO positive. A random sample of subjects was also tested for thyroid antibodies with 13.9 % of women and 2.9 % of males being anti-TPO positive; unlike most other studies, the prevalence did not increase with age.

Denmark In 1987–1988, the rates of overt hypothyroidism (elevated serum TSH and reduced serum thyroid hormone levels) were assessed in the moderately iodine-deficient region of East Jutland, Denmark [22]. Assuming that the cases of spontaneous hypothyroidism were autoimmune, incidence rate in females was 19.9 cases/100,000/year versus 3.1 cases/100,000/year in men. The incidence of hypothyroidism steadily increased from 30 years of age reaching a plateau in over 70 years.

A sample of 2,656 Danish adults aged between 41 and 71 years from Copenhagen were investigated for thyroid disorders in 1993–1994 [23]. The prevalence for positive TPO antibodies was 16.9 % in women and 6.6 % in men. Positive TPO titer was associated with advanced age (from 8.9 % in the youngest age group to 14.8 % in the oldest age group; $P = 0.02$), higher TSH (83 % of those with serum TSH > 5 mU/L vs. 10.3 % of those with normal serum TSH), and higher urinary iodine excretion (OR for positive TPO titer in those with high urinary iodine excretion [>150 μg/day] compared to low urinary iodine excretion [<70 μg/day] = 1.47; 95 % CI: 1.1–2.0).

The recent Danish investigation on iodine intake and thyroid disease (DanThyr) study has provided a wealth of epidemiologic data, and continues to publish important insights into the causes of thyroid disease [24–33]. The DanThyr is a comparative study of 2 regions of Denmark (the mildly iodine-deficient region of Copenhagen, and the moderately deficient region of Aalborg, located in North Jutland) before and after the national iodine fortification program (1999–2000). The investigators have performed three parallel studies: (1) a population-based prospective registry of the incident cases of hypo- and hyperthyroidism covering 550,000 people; (2) a cohort of 4,649 subjects commenced pre-fortification; and (3) a cohort of 3,570 subjects commenced post-fortification. This mixed study design has advantages of both providing global perspective on disease incidence and allowing focused hypothesis testing of exposure-outcome relationships. On a population level, much lower incidences of spontaneous hypothyroidism (confirmed autoimmune [30]) were found pre-iodization than seen in the iodine-replete UK studies; consistent with this finding were differential incidences between areas of mild-moderate iodine deficiency and more iodine-replete areas [27]. The age-standardized pre-iodization rate of spontaneous hypothyroidism for the whole population was 44.4 cases/100,000/year (95 % CI: 40.4–48.5) in women and 11.9 cases/100,000/year (9.8–14.0) in men, which appears higher than the previous East Jutland study (Fig. 1). The incidence of spontaneous hypothyroidism rose markedly with age. Comparing the regions of differential iodine status, the pre-iodization standardized incidence rate ratio for spontaneous hypothyroidism in Copenhagen vs. Aalborg was 1.53 (95 % CI: 1.29–1.80). In 2004–2005, the post-iodization incidence of overt hypothyroidism increased by a statistically significant 20 % in females and 40 % in males. In the 10 years after 1997, nationwide incident levothyroxine prescription rate nearly doubled [34].

Thyroid antibody status has been the main outcome measure in the smaller DanThyr cohort analyses. These were common pre-iodization with 14.5 % of women (approximately equally divided between ages of 18–22 years, 25–30 years, 40–45 years and 60–65 years) [25, 28] and 7.3 % of men aged 60–65 years harboring anti-TPO antibodies [25]. Again, the prevalence of antibody positivity increased with increasing age. Interestingly, there was no

prevalence difference between the regions. The investigators did not find any association between positive antibody status and parity [28]. Smoking was associated with a lower prevalence of Tg antibodies; to a lesser extent, a lower prevalence of TPO antibodies [32]. Post-fortification, the prevalence of thyroid antibodies, was significantly higher (Supplemental Table 2; $P < 0.001$) [33].

Other European studies

Spain Galofré et al. [35] studied a sample of the population of Vigo in Northwest Spain between 1990 and 1992 to estimate incidence of thyroid disorders. By a definition for autoimmune hypothyroidism of serum TSH level >5 mU/L plus the presence of positive antibodies, the incidence of autoimmune hypothyroidism was 47.1 cases/100,000/year (95 % CI: 29.2–65.1) in women and 2.1 cases/100,000/year (95 % CI: 0.0–6.4) in men.

Italy The Pescopagano survey was a comprehensive study of thyroid disease in a southern Italian village known to be iodine-deficient [36]. The study is notable for its use of ultrasound assessment and several important findings. By means of a definition of antibody positivity that required the presence of both TPO and Tg antibodies, 17.3 % of women and 7.0 % of men were considered positive. Prevalence progressively increased from childhood to the age 46–55 years and stayed relatively constant thereafter. Diffuse autoimmune thyroiditis was diagnosed by the presence of both high antibody titer and hypoechogenic ultrasound, and occurred in 4.9 % of females and 1.9 % of men.

Germany The Study of Health in Pomerania (SHIP) was conducted between 1997 and 2001 in a previously iodine-sufficient area in Northeastern Germany [37–39]. 3,941 participants aged 20–79 years were assessed for thyroid disorders. Like the Pescopagano survey, ultrasound assessment was performed on study participants. The prevalence of antibody positivity was much lower than in other studies (7 % of participants had elevated TPO antibodies) [37]. When autoimmune thyroiditis was defined as high antibody levels and hypoechogenic ultrasound, the prevalence was 1.2 %. Other important findings from this study were the association of autoimmune thyroiditis with occupational radiation exposure (OR = 3.46 [95 % CI: 1.16–10.31] [38] and with gravidity (OR 4.6 [95 % CI: 1.4–15.1]) [39]. With regard to the pregnancy findings, it is possible that the positive result in this study reflects the more specific definition that included an abnormal echo pattern on ultrasound than the one used in previous investigations where no relationship was seen.

Slovenia A recent Slovenian study complements the DanThyr data with regard to increased community iodine intake [40]. Salt iodization was strengthened nationwide in 1999 to shift the Slovenian population from mildly iodine-deficient to iodine-sufficient. Hashimoto's thyroiditis was diagnosed on the basis of positive thyroid antibodies and hypoechoic thyroid ultrasound. An incidence rate ratio for all Hashimoto's thyroiditis of 2.27 (95 % CI: 2.08–2.48) was seen in 2009 compared to the baseline year of 1999, and was 1.86 (95 % CI: 1.64–2.12) for Hashimoto's thyroiditis patients who were also hypothyroid (Fig. 1).

North America (United States)

Two studies of historic interest were performed in the USA before the onset of clinical antibody testing, when thyroid autoimmunity was assumed to be rare. Furszyfer et al. [41, 42] documented all Hashimoto's disease diagnoses in Olmsted County, Minnesota, from 1935 to 1967. While recognition in males remained uncommon, the incidence in females rose steadily throughout the study period from 6.5 cases/100,000/year in 1935–1944 to 69 cases/100,000/year in 1965–1967. Masi [43] performed a community-wide study of histologic Hashimoto's disease diagnoses in Baltimore from 1955 to 1960, finding marked racial differences (for example 9.6 cases/100,000/year in white females compared to 2.16 cases/100,000/year in black females). While it could be argued that differential access to healthcare may have accounted for these differences in surgical diagnosis, a concurrent autopsy survey gave consistent findings.

The third National Health And Nutrition Examination Survey (NHANES III) was conducted between 1988 and 1994 with the aim of generating representative health and nutritional information for the US population. Four papers relevant to autoimmune thyroid disease have analyzed data from approximately 17,000 people over the age of 12 years [44–47]. Positive TPO antibodies were demonstrated in 17 % of females and 8.7 % of males [44]. The prevalence increased with age and varied with race (highest in whites, lower in Mexican Americans, and lowest in blacks). Hypothyroidism, both clinical and overall, was strongly associated with TPO antibodies (ORs = 39.7 [95 % CI: 11.6–136.1] and 8.4 [95 % CI: 5.8–12.1], respectively. Abnormalities in thyroid function followed the same gender, age, and racial pattern. The gender relationship was lost when controlling for TPO antibodies [46]. In the antibody-negative population, serum TSH concentration rose with increasing age [47] although in another analysis, when age-race subgroups with similar prevalence of antibody positivity were compared (e.g., 20–29 year old whites and Mexican Americans vs. blacks aged 40–49 years), the 95th percentile for serum TSH became comparable [46]. Non-smokers had a greater prevalence of antibody

positivity than smokers (18 % vs. 11 % [95 % CIs 17–19 % vs. 10–13 %]), and smokers had a lower prevalence of raised serum TSH than non-smokers (2.6 %, vs. 5.57 [95 % CIs 2.0–3.2 % vs. 4.7–6.3 %]). [45].

Australia

The Busselton Health Study from Western Australia is a longitudinal health survey of a homogeneous rural Caucasian community that began in 1966. Data for serial cross-sectional antibody prevalence have been published (albeit using different assays without standardization) [48–52], as well as longitudinal follow-up data, from 1981 to 1993 [53]. In 1969, approximately 9 % of the sampled population were positive for thyroid epithelial cell antibodies (measured with immunofluoresence) [48]. In 1975, 9.8 % of females and 2.8 % of males were found to positive to thyroid microsomal antibodies measured via indirect immunofluorescence [49, 50]. TPO antibodies were measured by enzyme-linked immunoassay for analysis of the 1981 cohort with 17 % of females recorded as positive compared to 6.8 % of males (11.9 % overall out of 2,101 subjects) [52]. In female patients, no relationship was found between previous pregnancy and either antibody positivity or abnormal serum TSH [51]. 81 % of living patients from the 1981 cohort were reassessed in 1994. Consistent with the cohort's older age at reassessment, 15.1 % were TPO positive in 1994. By means of a cut-point of TSH > 10 mU/L to define "overt" hypothyroidism, which is not the standard definition, a cumulative incidence of 3.5 % was found for the study period. Comparing to other studies, and assuming a constant rate of overt hypothyroidism, this is 273 cases/100,000/year. In women with positive thyroid antibodies (TPO or Tg), the prevalence of hypothyroidism at follow-up was 12.0 % (95 % CI: 3.0–21.0 %) when baseline TSH was 2.5 mU/L or less, 55.2 % (95 % CI: 37.1–73.3 %) for TSH between 2.5 and 4.0 mU/L, and 85.7 % (95 % CI: 74.1–97.3 %) for TSH above 4.0 mU/L.

North Asia

Japan

The first published Japanese study found that the microsomal antibody prevalence was 10.2 % in women and 6.0 % in men [54]. A study from Hisayama of adults aged over 40 years found microsomal antibodies in 14.2 % of women and 7.2 % of men [55]. Working age people from an area of excessive iodine intake (lowest recorded urinary value = 245 μg/L) were found to have combined antibody prevalence of 13.9 % for women and 6.5 % for men [56]. No difference in urinary iodine concentration was found between antibody-positive and -negative people. A study in Okinawa also assessed antibody prevalence in relation to iodine nutrition [57]. Again, the populations studied were either iodine-sufficient or excessive. Very high prevalence rates were found, but did not differ with respect to iodine intake.

China

A Chinese group has extensively investigated the effect of variation in iodine status on thyroid disease [58–60]. The research program examined thyroid disease in 3 counties with differing iodine nutrition—Panshan (mildly iodine-deficient), Zhangwu (more than adequate iodine nutrition), and Huanghua (excessive iodine intake). 3,761 subjects aged over 13 years were initially assessed in 1999 with 80.2 % re-examined 5 years later. By a definition of autoimmune thyroiditis of elevated serum TSH and positive antibody status, the baseline 0.5 % prevalence in Panshan was significantly lower than that in Zhangwu (1.8 %) and Huanghua (2.8 %) with the difference between Zhangwu and Huanghua of borderline significance ($P = 0.06$). Converting the population cumulative incidence of autoimmune thyroiditis to yearly incidence, the rate in Panshan was 40 cases/100,000/year, compared to 200 cases/100,000/year in Zhangwu and 260 cases/100,000/year in Huanghua (a statistically significant difference between Panshan and other regions was present, but no significant was apparent between Zhangwu and Huanghua) [59]. Baseline prevalence of both subclinical (elevated serum TSH but normal free thyroxine) and overt hypothyroidism (elevated serum TSH and reduced serum free thyroxine) increased with population iodine status; in those above 45 years of age, prevalence of Tg antibody was highest in Huanghua ($P = 0.016$ compared to Panshan and $P = 0.029$ compared to Zhangwu) [60]. For patients with initially euthyroid but with positive antibodies, the cumulative incidence of new elevated TSH was the greatest in Huanghua followed by Zhangwu and Panshan although higher antibody titer was not associated with future elevated TSH. Assessing baseline TSH alone, the lowest risk of subsequent abnormal serum TSH was seen when baseline levels were 1.0-1.99 mU/L with the risk of hyperthyroidism in those with lower baseline serum TSH and hypothyroidism in those with higher baseline serum TSH.

Another recent Chinese study also assessed two regions with differing iodine intakes [61]. In an area of more than adequate iodine intake (median urinary iodine concentration 261 μg/L), 10.6 % of subjects were TPO positive. In the area of adequate iodine nutrition (median urinary iodine concentration 145 μg/L), 8.4 % of subjects were TPO positive, a statistically significant difference ($P = 0.02$).

Graves' disease

Europe

UK

Two UK studies assessing Graves' disease incidence concluded in early 1980s. In 1982, all cases of thyrotoxicosis were documented in 7 towns with Graves' disease diagnosed using TSH-receptor antibodies [62]. Graves' disease incidence was 15 cases/100,000/year with peak age-specific incidence highest between ages 40-50 years. The other study was a 10-year study in Staffordshire concluding in 1983 [63]. The average incidence over the course of the study was 15.9 cases/100,000/year (25.8 cases/100,000/year in women vs. 5.5 cases/100,000/year in men). The highest age-specific incidence was seen in the 45–55 year age group. Interestingly, the incidence appeared to rise over early years of the study and then decreased somewhat later ($P_{\text{linear trend}}$ remained significant < 0.025).

The Whickham study also collected hyperthyroidism data at the 20-year follow-up [12]. From the surviving females, 10 new cases of Graves's disease were identified (including 3 at the time of follow-up). Assuming a constant rate throughout the 20-year study, the incidence can be calculated as 50 cases/100,000/year. There were no new cases in men.

Nordic countries

Again, the greatest number of studies comes from Nordic countries. These studies provide the best evidence on trends over time.

Iceland Two early Icelandic studies attempted to capture nationwide diagnoses of thyrotoxicosis. The first used hospital records to capture cases and covered the period of 1938–1967 [64]. The incidence of Graves' disease ranged from 9.7 cases/100,000/year to 13.8 cases/100,000/year across the period of study. The second study (1980–1982) surveyed practitioners likely to encounter thyrotoxicosis as well as querying hospital records [65]. The annual incidence was 19.3 cases/100,000/year with the majority of cases between 20 and 49 years of age. Unfortunately, because of the possibility of incomplete case documentation in hospital-based studies, it is unclear whether the increased incidence reported in the second study was an accurate estimate.

Sweden Six Swedish studies have been reported with one city (Malmö) being repeatedly assessed (Fig. 2). The first Malmö study examined the 1970–1974 period [66] with the Graves' disease incidence being 17.7 cases/100,000/year (27.2 cases/100,000/year in women and 7.4 cases/100,000/year in men). By 1988–1990, the incidence of Graves' disease was 22.3 cases/100,000/year (34.4 cases/100,000/year in women and 8.8 cases/100,000/year in men) [67]. Across the two-time periods, there was a statistically significant increase in incidence in women aged less than 50 years ($P < 0.01$). The most recent study assessing Graves' disease in Malmö was a part of a wider Swedish study conducted in 2003–2005 [68–70]. The incidence in Malmö was higher than for any other city (29.6 cases/100,000/year compared to an average of 21.0 cases/100,000/year overall with the lowest incidence of 16.7 cases/100,000/year in the cities of Eskilstuna and Katrineholm). The majority of Graves' disease cases in this study were recorded in the range 30–69 years of age. Comparing 2003–2005 with 1988–1990, the increased incidence in Malmö was statistically significant ($P = 0.0051$). The age-specific incidence in Malmö was highest in the 50–59 years age group (also reflected in the wider study where the majority of cases occurred between ages 30 and 69 years). Of the Swedish studies not assessing Malmö, one was performed in Jämtland between 1975 and 1984 and the other in central Sweden between 1987 and 1989. The Jämtland study found a mean incidence of 16.6 cases/100,000/year without a trend over time, during a period where the incidence of toxic nodular disease decreased significantly [71]. The 1987–1989 study found an incidence of 12.7 cases/100,000/year [72]. This paper also documented increased risk of Graves' disease among those who had experienced stressful life events.

Denmark Two Danish studies have addressed Graves' disease incidence (Fig. 2). The first was performed in East Jutland from 1987 to 1988 [73], reporting an incidence of 14.8 cases/100,000/year. The second study was the DanThyr study described earlier [74]. Thus far, the investigators have reported Graves' disease incidences for the pre-iodization period from 1997 to 2000. The combined standardized Graves' disease incidence (distinguished from other causes by TSH receptor antibodies or non-suppressed homogeneous thyroid scintigraphy) was 31.2 cases/100,000/year (95 % CI: 26.4–35.9) with a 4.5 times higher rate in women compared to men. When comparing the moderately iodine-deficient Aalborg to mildly deficient Copenhagen, the standardized incidence rate ratio did not meet statistical significance (1.2; 95 % CI: 0.99–1.40). Age-specific incidence rates were constant from age 30 to 80 years of age.

Other European studies

Switzerland The influence of community iodization was investigated in Solothurn, Switzerland [75, 76]. This study was based at a single hospital, and Graves' disease was

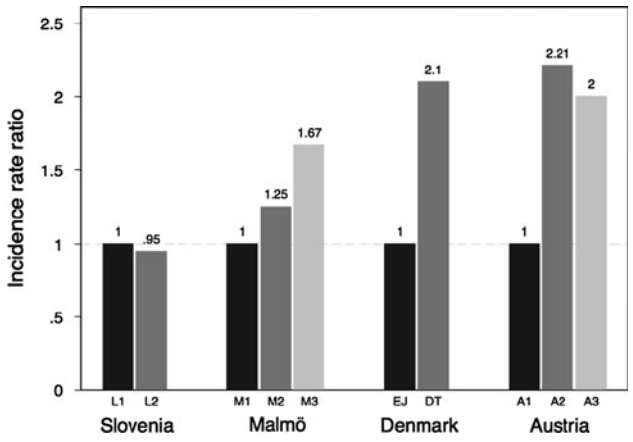

Fig. 2 Crude incidence rate ratios (IRR) for Graves' disease reported in studies performed in similar geographic locations since 1970. The baseline studies (Incidence Rate Ratio [IRR] = 1) are the first studies performed in each region. IRR for *L2* versus *L1* is not statistically significant (95 % confidence interval: 0.81–1.13). IRR for M2 versus M1 is not statistically significant. IRR for M3 versus M2 is statistically significant ($P = 0.0051$). Statistical significance for EJ vs. DT cannot be determined from published data. IRR for A2 versus A1 is statistically significant (95 % confidence interval: 2.04–2.39). *L1* Ljubljana (1999), and *L2* Ljubljana (2009) [40]. *M1* Malmö (1970–1974) [66]. *M2* Malmö (1988–1990) [67]. *M3* Malmö (2003–2005) [69]. *EJ* East Jutland (1987–1998) [73]. *DT* DanThyr study (1997–2000) [74]. *A1* Austria (1987–1989), *A2* Austria (1993), and *A3* Austria (1995) [79]. *Note* another study (Paunkovic et al. [78]) found too large an IRR increase over time to be presented in this figure

diagnosed via thyroid scintigraphy. When compared to the control period of 1978–1979, the investigators found an initial increase in diagnoses, followed by a decline with an incidence of 20.6 cases/100,000/year for the final 2 years of the study (1995–1996). There are three reasons to be cautious about this study. First, there were several periods of volatility in incidence through the study period, and the control period was short. The authors themselves consider the possibility of misclassification of cases in the early study period, increasing the apparent incidence of Graves' disease. Furthermore, the incidence figures rely on the assumption that no other providers were diagnosing and treating patients in the catchment area.

Spain The difficulties in using hospital-based records are illustrated in two studies performed in Vigo, Northwest Spain [35, 77]. The first was a hospital-based study of incidence before and after an iodization program [77]. Pre-iodization (1977–1984), the incidence of Graves' disease, was calculated to be 2.65 cases/100,000/year rising to 6.43 cases/100,000/year post iodization (1985–1989; $P < 0.05$). The second study was conducted immediately after the first, but with a case-finding approach using laboratory data [35]. Almost all cases of Graves' disease manifested overt thyrotoxicosis. The 1990–1992, point estimates for Graves' disease incidence were 41.9 cases/100,000/year (95 % CI: 25.0–58.8) for women and 2.1 cases/100,000/year (95 % CI: 0–6.4) for men (22.2 cases/100,000/year [95 % CI: 14.7–33.7] overall). It seems likely that large increase in apparent incidence between the first and second studies is due to more complete case ascertainment in the latter period rather than a true change in epidemiology.

Serbia The potential role of stress on Graves' disease is highlighted by a 25-year study from the Timok region in Eastern Serbia [78]. Recorded incidence rose from 5.56 cases/100.000/year in 1971–1980 to 11.7 cases/100,000/year in 1981–1990 before increasing dramatically to 45.3 cases/100,000/year in 1996. While the first decade's data may be incomplete, data integrity later in the study was improved. No change in incidence of toxic adenoma was seen throughout the study period. It seems possible that population hardship (economic deprivation associated with international sanctions and nearby civil war) occurring during the early 1990s contributed to the rising incidence although other causes such as altered iodine intake cannot be ruled out.

Austria Graves' disease incidence before and after a salt iodization program was assessed in Austria from 1987 to 1995 [79]. Graves' disease incidence (both overt and subclinical disease) doubled throughout the study period, from a baseline of 12.2 cases/100,000/year to a peak of 27.0 cases/100,000/year in 1993, and remained at similar incidence of 24.4 cases/100,000/year at the end of the study (Fig. 2). When overt Graves' disease was considered separately, the relative increase was nearly identical to the overall Graves' disease increase.

Slovenia No difference in Graves' disease incidence rate was seen in 10 years following a 1999 increase in salt iodization in Slovenia (incidence rate ratio 0.95 [95 % CI: 0.81–1.13]; Fig. 2) [40]. In mid-study, the incidence rate spiked although this appeared to be due to increased sensitivity in a new TRAb assay, and the incidence rate settled back to baseline thereafter.

North America

In addition to documenting the incidence of Hashimoto's disease in Olmsted County, the Mayo Clinic group also described the frequency of Graves' disease diagnosis between 1935 and 1967 [42, 80]. The incidence was constant throughout the study period, estimated to be 30.5 cases/100,000/year in females and 8.0 cases/100,000/year in men.

The Nurses' Health Study II included 115,109 women aged 25–42 years at entry and documented diagnoses of

Graves' disease from 1989 to 2001 [81]. Assuming a constant rate over that time, the Graves' disease incidence rate would be 38.3 cases/100,000/year (460 cases/100,000 women over 12 years). Smoking was associated with an increased hazard ratio for diagnosis with a dose–response relationship apparent for increasing the numbers of pack years smoked. The hazard for Graves' disease decreased with the number of years since quitting smoking. Inconsistent results were found in relation to body mass index and Graves' disease risk.

China

The Panshan, Zhangwu, and Huanghua study mentioned earlier also collected data on Graves' disease [59, 82, 83]. Assuming a constant incidence rate throughout the 5-year study period, very high incidences were found: 160 cases/100,000/year in the mildly iodine-deficient Panshan; 120 cases/100,000/year in the more than adequately iodine-replete Zhangwu; and 120 cases/100,000/year in the excessively iodine-replete Hwangha (none of these values were statistically significantly different). The same investigators also retrospectively assessed hyperthyroid diagnoses for the period before the prospective study, which also coincided with iodine supplementation in Zhangwu and Huanghua. No statistically significant difference in hyperthyroidism diagnoses occurred in either of these sites (while subtypes were not distinguished, Graves' disease accounted for the majority of diagnoses overall).

Synthesis and conclusions

This review has documented studies that assess the incidence and prevalence Hashimoto's disease, Graves' disease, and thyroid autoimmunity. A systematic search strategy was used to identify relevant studies, and describe the results grouped by disease, geographic region, and time period. In this way, we hoped to identify patterns of incidence and prevalence, some potentially relevant environmental factors that may influence disease epidemiology, and document barriers to definitive conclusions being drawn.

The strongest conclusions that can be made include the following: (1) women have a much greater risk of autoimmune thyroid disease (both Hashimoto's and Graves' disease) than men; (2) there is substantial geographic variation in the diagnosis of both autoimmune thyroid diseases (Figs. 3, 4), and thyroid antibody prevalence differs with race (although there is a lack of data on Graves' disease incidence by racial origin); (3) hypothyroidism from Hashimoto's disease causes the majority of clinical disease and becomes more common with advancing age; (4) thyroid antibodies are very common, their frequency increases with age, and are associated with the eventual development of hypothyroidism (although there are a few studies that show a peak of antibody positivity around 45–55 years); (5) spontaneous (presumed autoimmune) hypothyroidism becomes more frequent with age (Fig. 5); (6) populations that are iodine-sufficient, compared to those that are iodine-deficient, appear to have higher incidences of

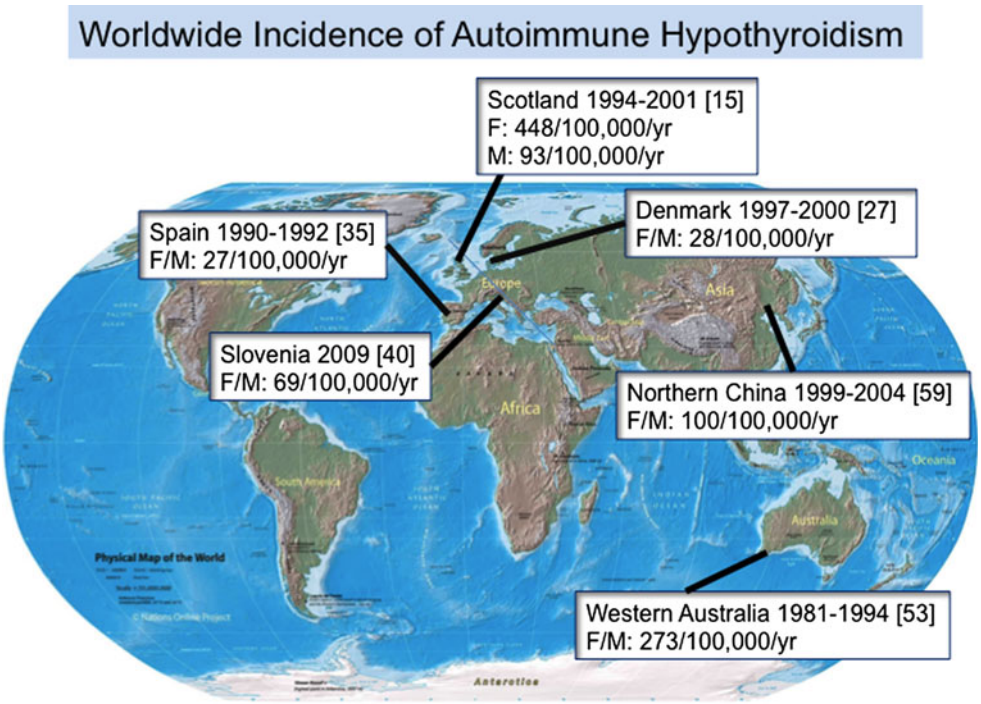

Fig. 3 Worldwide reported incidence of autoimmune hypothyroidism. The incidence data are taken from the recent studies in each region. While diagnostic criteria differed slightly in each study, this is unlikely to account for the very large differences between regions. *Note*: The subjects included in the Northern China study [59] were 75 % female, hence an incidence of 100/100,000/year for the entire population is likely an overestimate

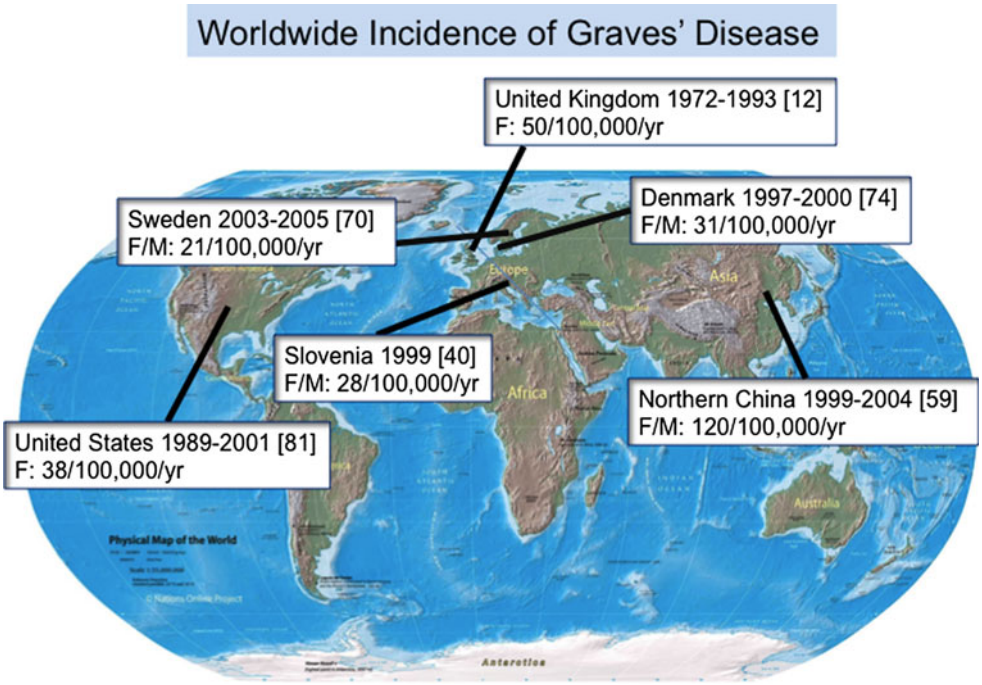

Fig. 4 Worldwide reported incidence of Graves' disease. The incidence data are taken from the recent studies in each region. *Note*: The subjects included in the Northern China study [59] were 75 % female, hence an incidence of 120/100,000/year for the entire population is likely an overestimate

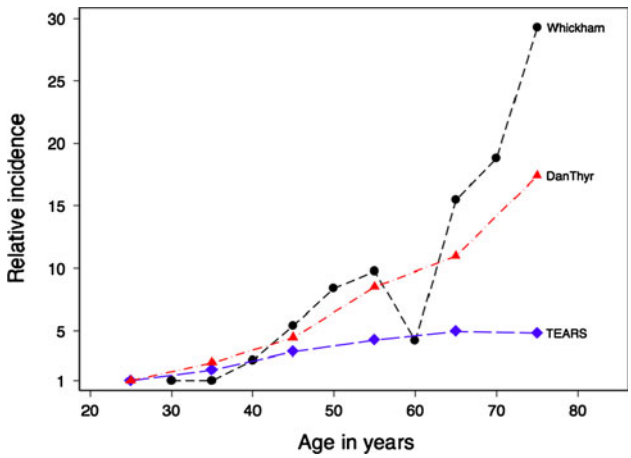

Fig. 5 Age-specific relative incidence of spontaneous hypothyroidism in three studies. The incidence is depicted relative to a baseline incidence level for each study. Data are taken from the Wickham study (women; 1972–1993) [12], TEARS (women; 1993–1996) [14], and the DanThyr study (both sexes; 1997–2000) [27]

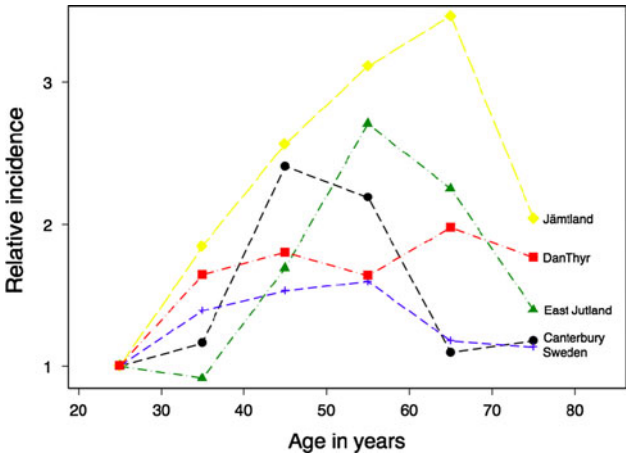

Fig. 6 Age-specific relative incidence of Graves' disease in five studies. The incidence is depicted relative to a baseline incidence level for each study. Data are taken from Jämtland, Sweden (1975–1984) [71], Canterbury, New Zealand (1983–1985) [84], East Jutland, Denmark (1987–1988) [73], the DanThyr study (1997–2000) [74], and the Swedish Thyroid Study (2003–2005) [70]

hypothyroidism and probably more thyroiditis; but, at excessive levels of iodine nutrition there is no consistent evidence for additional impact; (7) moving a population from iodine-deficient to -sufficient increases thyroid antibody prevalence and hypothyroidism; (8) Graves' disease also has age-related changes in incidence although they are marked compared with Hashimoto's disease (Fig. 6); and (9) smoking is associated with a higher incidence of Graves' disease, but a lower prevalence of positive thyroid antibodies.

Owing to the trends over time, the contemporary reported crude incidence rates of Hashimoto's disease and hypothyroidism are higher than in studies previously performed in comparable regions (Fig. 1). Unfortunately, it is impossible to know whether this is due to actual increased incidence or factors related to study design. The two studies that showed a definite increase in hypothyroidism incidence were both in the setting of recent iodization programs [31, 40]. Several Graves' disease studies

Box 1 Barriers in comparing incidence and prevalence studies

Study populations
Study populations rarely comparable
Genetic factors
Environmental factors (e.g., iodine intake)
No standardization for age/race/gender among studies
Disease definition
Diagnostic methods vary between eras
Pre-clinical disease definitions non-standardized (e.g., autoimmune thyroiditis sometimes diagnosed clinically, or via antibodies, or via antibodies and biochemically, or antibodies and ultrasound hypoechogenicity)
Clinical disease terminology non-standardized (e.g., overt hypothyroidism may mean clinically recognized hypothyroidism or biochemical hypothyroidism with elevated serum TSH and decreased serum thyroid hormone)
Laboratory
Assay techniques vary among eras
No standardization of assays even when similar techniques used
No standardization of positive cut-points
Study design
Methods of case identification differ (e.g., case-finding studies from hospitals vs. laboratory identification vs. self-reports)
Effects of altered diagnostic or therapeutic decision making are not able to be teased out
Serial studies in same population addressing these issues are rare

presented in Fig. 2 also provide evidence of an increasing incidence (with the most directly comparable studies coming from Malmö [66, 67, 69, 70]) although there are only a few studies where results are directly comparable. We have summarized the barriers to making comparisons between current studies in Box 1.

Our main aim was to not only comprehensively review the literature for the incidence and prevalence of autoimmune thyroid disease, but also to set inclusion criteria such that comparison of these measures was meaningful. Thus, we omitted exclusively pediatric (very low occurrence) and geriatric (very high occurrence of hypothyroidism) studies, recognizing that this may detract from the completeness of our review. Interested readers can refer to the McGrogan et al. [5] and Vanderpump [6] reviews, which catalog several of these studies. Because of the richness of epidemiologic data in the included studies, we have also highlighted important ancillary findings in addition to providing actual incidence or prevalence figures. We feel this adds context to the study descriptions and summarizes valuable knowledge. The only problem with this approach is that we have intentionally excluded several study design types that are useful for detailed risk factor assessment, including case-control studies and twin studies.

The question of changing disease patterns is not merely academic. Understanding the epidemiology of autoimmune thyroid disease, including its geographic differences and environmental influences, will provide clues to finding its etiology, allow estimation of changes in epidemiology of associated conditions (e.g., the possible association with thyroid cancer), and provide data for health utilization projections into the future. Autoimmune thyroid disease is common, and there are hints in the literature that its occurrence may be changing. Well-designed longitudinal studies are required to address this question.

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Conflict of interest The authors declare that they have no conflict of interest.

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